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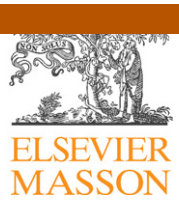

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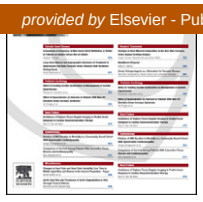

SCIENTIFIC EDITORIAL

New/actual cardiac biomarkers in patients with suspected acute myocardial infarction: Are we close to identifying the 'Holy Grail'?

Biomarqueurs cardiaques récents chez les patients suspects d'infarctus du myocarde : pouvons-nous espérer atteindre le Saint Graal ?

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The daily challenge for physicians in emergency departments (ED) relies on a combination of risk stratification and diagnostic procedures, thereby allowing optimal triage of patients. Biomarkers are key in the triage of patients with suspected acute myocardial infarction (AMI); finding the best interpretation provided by a biomarker (or a combination of biomarkers) is therefore crucial. If poorly sensitive, information provided by a biomarker will lead to a hazardous discharge and therefore a high risk of adverse events. Conversely, poor specificity will lead to the admission of a large number of low-risk patients, further increasing the use of healthcare resources.

Over the past decade, cardiac biomarkers (other than troponins) have been the topic of intense medical research. If the cardiospecificity of cardiac troponins (cTn) has never been questioned, the main objective of exploring new candidates is to find a way of increasing sensitivity for the diagnosis of AMI. Indeed, many articles reported the possible high merit of some new candidates, which provided additive information corresponding to specific pathophysiological pathways including, for example, inflammation, endogenous stress and plaque rupture in acute myocardial infarction (AMI) [1—3]... Very recently, some research

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groups have focused on the recently developed sensitive assays for cTn, which can detect very low circulating cTn concentrations and allow precise determination of the 99th percentile in the general population. While there was growing literature about their increased sensitivity to detect AMI, [4—6] there was also growing scepticism among clinicians as to whether these sensitive assays are associated with a clinically significant improvement in comparison with conventional (i.e. non-sensitive) cTn assays. Yet, the key questions about new assays may be, for example: is the principal objective to determine the risk profile of a population or to assess individual risk? What is the overall improvement of increased sensitivity offered by these new assays after integration of the associated cost: decreased specificity? Are these sensitive assays clinically helpful? That is, will they help clinicians improve patient outcomes, and are other early markers of myocardial injury redundant? If the answer is yes, how should clinicians incorporate these assays into clinical practice? If the answer is no, how do we reach the ''Holy Grail''?

It is easy to answer to the first question: clinicians will be largely interested in individual risk stratification. There are a ''myriad'' of existing risk stratifications tools and indexes; one should keep in mind that the most powerful indexes are based on a combination of data, including clinical, electrocardiographic and biological measurements. As a consequence, the demonstration that one of the most powerful tools used for risk stratification — the GRACE risk score — is neither affected nor improved by the incorporation by new biomarkers, such as natriuretic peptides or sensitive cTn assays might be expected [7]. In addition, we should be aware that we always analyse the risk information offered by these scores in the context of the results of clinical trials, which unfortunately predominantly randomize low-risk patients.

The possible benefit offered by a new test is hard to determine, as most of the studies are retrospective or observational. However, existing data clearly suggest that sensitive cTn assays offer better and earlier identification of patients with AMI, and the balance of a true positive in patients newly identified with an AMI through these sensitive assays is not counterbalanced by over-identification of patients without an AMI but with elevation of cTn [4,6,8]. The study by Mills et al. published in the *Journal of the American Medical Association* in 2011 is also very informative [9]. The authors studied 1038 patients with suspected AMI during the validation period, when decisions were based on contemporary cTn assays, and 1054 patients during an implementation phase when decisions were based on the results of sensitive cTn assays. The authors demonstrated that reducing the decision threshold (using a sensitive assay) was associated with a marked reduction in recurrent AMI/mortality (from 39% at 1 year, to 7%), when physicians were informed of the assay results and thus were able to modify management strategies accordingly [9].

How then to incorporate these new assays into standard care? And will the increased rate of patients with cTn elevation complicate triage procedures in emergency departments? On the one hand, there is clear evidence that mortality and AMI rates increase progressively with cTn concentrations above the 99th percentile. On the other hand, the unequivocal answer to ''cTn positivity'' should no longer be encouraged, as we will capture many patients who will have little to gain and perhaps even more to lose from invasive procedures. To illustrate this, we recently studied patients who presented to the emergency departments with acute chest pain and were discharged after serial measurements of contemporary cTn, but who had mild and stable elevation of high-sensitivity cTnT [10]. We confirmed the increase in intermediate- and long-term risk of death/AMI in these patients with mildly elevated cTn but showed that that the rate of 30-day events was very low; overall our data suggest that these patients are in need of further investigations and treatments, but not necessarily immediate hospitalization [10].

Although the development of sensitive cTn assays should be considered as a major improvement in the management of patients suspected of AMI and should be recommended for daily practice, there is still a long way to go before capturing the Holy Grail. In fact, controversies still exist about the best use of these assays; for example, the consideration of an absolute or relative change in cTn concentrations, the exact timing of serial measurement [11], and the algorithm to use in specific populations (e.g. patients with a history of cardiac disease or elderly patients). Furthermore, the initial benefit of some biomarkers in addition to conventional cTn assays needs be re-addressed and compared with sensitive cTn assays; one can speculate that some, but not all, will fail [12—14]. The use of reclassification indexes should be encouraged in these future studies [15].

To conclude, the development of sensitive assays of cTn measurement is highly clinically significant, but only if clinicians interpret the results appropriately [16]. The cut-off value should be set at the level of 99th percentile value; minor elevations of cTn have broad possible origins, including acute (possibly myocardial ischaemia) and chronic cardiac disorders. Importantly, they have prognostic significance. More highly elevated cTn concentrations more often correspond to AMI, but alternative cardiac diagnoses do exist.

Disclosure of interest

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